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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/075,954	02/13/2002	Charles Andrianjara	A0000476-01-CFP	9823
28880	7590	02/25/2005	EXAMINER	
WARNER-LAMBERT COMPANY 2800 PLYMOUTH RD ANN ARBOR, MI 48105			TRUONG, TAMTHOM NGO	
			ART UNIT	PAPER NUMBER
			1624	

DATE MAILED: 02/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/075,954

Applicant(s)

ANDRIANJARA ET AL.

Examiner

Tamthom N. Truong

Art Unit

1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 10 December 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3,4,9,12-15,29 and 37-39 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 1 and 15 is/are allowed.
- 6) ☒ Claim(s) 3,4,9,12-14,29 and 37-39 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>9-13-04</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's election of group 10 in the response of 12-10-04 is acknowledge. The election is traversed on the ground that claims 4, 14, 15 and 29 be included in group 10. Said traversal is found persuasive since those claims depend on claim1, and claim 1 has been amended to recite only the elected group 10. Claim 15 has also deleted non-elected species.

Claims 2, 5-8, 10, 11, 16-28, and 30-36 have been cancelled. Note, in the claim, applicant indicates claim 30 and 36 cancelled; however, in the remark, claims 30 to 36 are listed as cancelled. Clarification is solicited.

Therefore, the elected group 10 is revised to include claims 1, 3, 4, 9,12-15, 29 and 37-39, which are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 3, 4, 9, 12-14, 29 and 37-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:
 - a. Claims 3, 4, 9, 12-14 and 37-39 recite the term "*characterized*" which is unclear if the limitations followed said term are part of the claims.

b. Claim 29 is an improper dependent claim because it depends on claim 11 which has been cancelled. Since claim 11 has been cancelled, it is difficult to ascertain the metes and bounds of the pending dependent claim.

c. Claim 37 is an improper dependent claim because it depends on claim 11 which has been cancelled. Since claim 11 has been cancelled, it is difficult to ascertain the metes and bounds of the pending dependent claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. **Scope of Enablement:** Claims 37-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of adult periodontal disease, does not reasonably provide enablement for the treatment of arthritis, osteoarthritis, or rheumatoid arthritis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors have been considered in the determination of an enabling disclosure:

- (1) The breadth of the claims;
- (2) The amount of direction or guidance presented;

- (3) The state of the prior art;
- (4) The relative skill of those in the art;
- (5) The predictability or unpredictability of the art;
- (6) The quantity of experimentation necessary;

[See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int., 1986); also *In re Wands*, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)].

The breadth of the claims:

Claim 37 recites a “*method for treating a disease or complaint involving a therapy by inhibition of MMP-13 characterized in that the disease or the complaint is arthritis...*” which covers arthritis and perhaps other inflammatory diseases as well.

Claim 38 depends on claim 37 and recites the disease to be osteoarthritis. Again the term “*characterized*” is used, which makes it unclear if osteoarthritis is the only intended disease, or other diseases are also intended as well.

Claim 39 depends on claim 37 and recites the disease to be rheumatoid arthritis. Here too, the term “*characterized*” is used, which makes it unclear if osteoarthritis is the only intended disease, or other diseases are also intended as well

The amount of direction or guidance presented: The specification only describes the *in-vitro* activity of the compounds of Formula I on MMP-13, and provides IC₅₀. However, such an *in-vitro* activity does not warrant the *in-vivo* anti-inflammatory action for the treatment of osteoarthritis or rheumatoid arthritis. Furthermore, the specification does not provide an data such as increased motion range, or alleviation of joint and muscle pain to support the treatment

of arthritis. Therefore, the provided enablement is insufficient to guide the skilled clinician to use the claimed compounds in the treatment of osteoarthritis or rheumatoid arthritis.

The state of the prior art: Currently, MMP inhibitors are targeted for the treatment of adult periodontal disease, as there is no established data for using MMP inhibitors in the treatment of osteoarthritis or rheumatoid arthritis. According to the article of Greenwald, the failure of MMP inhibitors as therapeutic agents is because the *in-vitro* activity does not always warrant the *in-vivo* efficacy. Thus, with the guidance of Greenwald, the skilled clinician (at most) would only use the claimed compounds in the treatment of periodontal disease.

The relative skill of those in the art: Even with the advanced training, the skilled clinician would have to engage in undue experimentation to establish data that would adequately support the use of the claimed compounds in the treatment of osteoarthritis or rheumatoid arthritis. Such a task would require a tremendous amount of effort, time and resources.

The predictability or unpredictability of the art & The quantity of experimentation necessary: The pharmaceutical art has been known for its unpredictability due to various pathways, or biological factors that are sometimes genetically unique to individuals. In the instant case, the specification only shows *in-vitro* data for the inhibition of MMP-13. However, said evidence does not adequately guide the skilled clinician in the treatment of osteoarthritis or rheumatoid arthritis. Although osteoarthritis and rheumatoid arthritis are common diseases, treating them with potent agents could pose a high risk of osteoporosis as well as other unexpected side effects. Thus, with such a limited teaching, the skilled clinician would have to

carry out undue experimentation to use the claimed compounds in the methods recited in claims 37-39.

Allowable Subject Matter

3. Claims 1 and 15 are allowable.

The following is a statement of reasons for the indication of allowable subject matter:

Claim 1 recites a genus of substituted 2,4-dioxo-1,4-dihydro-2H-pyrido[3,4-d]pyrimidiny-3-yl having two side chains that are not taught or fairly suggested by the prior art of record. The closest prior art, **Edwards et. al.** (US 5,532,366 cited previously), compounds of 1,4-dihydro-2H-pyrido[3,4-d]pyrimidinyl. However, said compounds have three oxo groups. An update search yields the reference of **Bartroli et. al.** (US 5,807,854), which teaches a compound of pyrido[2,3-d]pyrimidine. There is no nexus between Edwards et. al. and Bartroli et. al. for a combined teaching to render obvious the claimed invention.

Claim 15 recites species that are not taught in any of the prior arts of record.

Specification

4. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification. Applicant is advised to especially check for hyperlinks, which are not allowed.

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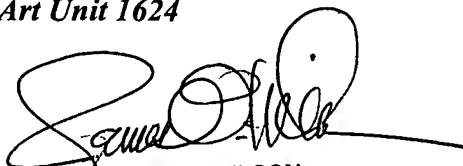
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tamthom N. Truong whose telephone number is 571-272-0676. The examiner can normally be reached on M-F (10:00-6:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


Tamthom N. Truong
Examiner
Art Unit 1624

2-17-05


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